

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	45	FLECKENSTEIN NEAR BERNHARD	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:31
L3	10	NEIPEL FRANK	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:31
L4	6319	(HHV-8 or herpes\$10) and (interleukin-6 or IL-6 or V-IL-6 or vIL-6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:40
L5	111	(HHV-8 or herpes\$10) WITH (interleukin-6 or IL-6 or V-IL-6 or vIL-6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:34
L6	7	(HHV-8 or herpes\$10) NEAR (interleukin-6 or IL-6 or V-IL-6 or vIL-6)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:33
L7	5	((HHV-8 or herpes\$10) WITH (interleukin-6 or IL-6 or V-IL-6 or vIL-6)).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:35
L9	13	ALBRECHT NEAR JENS-CHRISTIAN	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:36
L11	275	Chang Yuan	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	OFF	2005/03/28 13:37
L12	20	Hayward Gary	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	OFF	2005/03/28 13:38
L14	991	Nicholas John	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:39
L15	6	l11 and l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:40
L16	1	l12 and l5	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:40

L17	1	I14 and I5	US-PGPUB; USPAT; EPO; JPO; DERWENT	NEAR	ON	2005/03/28 13:40
L22	153	(interleukin-6 or IL-6 or V-IL-6 or vIL-6) NEAR (interleukin-6 or IL-6) NEAR receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:43
L23	1	(V-IL-6 or vIL-6) NEAR (interleukin-6 or IL-6) NEAR receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:44
L24	3	(V-IL-6 or vIL-6) SAME (interleukin-6 or IL-6) NEAR receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:44
L25	21	(US-20030211468-\$ or US-20040228838-\$).did. or (US-5849564-\$ or US-5854398-\$ or US-5861240-\$ or US-5861500-\$ or US-6060284-\$ or US-6174685-\$ or US-6177080-\$ or US-6183751-\$ or US-6264958-\$ or US-6348586-\$).did. or (EP-524421-\$ or EP-893504-\$ or US-5854398-\$ or US-5861500-\$ or WO-9803657-\$ or WO-9416062-\$).did. or (JP-06113858-\$).did. or (US-5831064-\$ or US-6183751-\$ or WO-9803657-\$ or US-6264958-\$ or US-5831064-\$). did.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/28 13:51

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(FILE 'HOME' ENTERED AT 13:54:42 ON 28 MAR 2005)

FILE 'MEDLINE, CANCERLIT, CAPLUS, SCISEARCH' ENTERED AT 13:55:04 ON 28 MAR 2005

L1 288 S (VIRAL INTERLEUKIN-6) OR VIL-6 OR V-IL-6
L2 30089 S ((INTERLEUKIN-6 OR IL-6) (L) RECEPTOR) OR IL-6R
L3 111 S L1 (L) L2
L4 40 DUP REM L3 (71 DUPLICATES REMOVED)
L5 1 S L4 AND PY<=1996
L6 40 FOCUS L4 1-
E FLECKENSTEIN BERNHARD?/AU
L7 144 S E1
L8 3 S E2
L9 147 S L7 OR L8
L10 3 S L9 AND L3
L11 3 DUP REM L10 (0 DUPLICATES REMOVED)

=> d an ti so au ab pi l11 1-3

L11 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:89360 CAPLUS
DN 128:166368
TI The interleukin 6 of human herpesvirus 8 and its use in diagnostics and therapeutics
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
IN Fleckenstein, Bernhard; Albrecht, Jens-Christian; Neipel, Frank; Friedman-Kien, Alvin; Huang, Yao-Qi
AB Human herpesvirus 8 is found to carry a gene for an interleukin 6 that can bind to the interleukin 6 receptor. The interleukin and the gene encoding can be used in the diagnosis and treatment of a number of diseases including: Kaposi sarcoma, Castleman's disease, multiple myeloma, kidney cell carcinoma, mesangial proliferative glomerulonephritis or B cell lymphoma. The protein may be manufactured by expression of the cloned gene.
PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9803657 A1 19980129 WO 1996-EP3199 19960719
W: US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
EP 912742 A1 19990506 EP 1996-927558 19960719
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE
US 2004228838 A1 20041118 US 2004-828343 20040421

L11 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:184856 CAPLUS
DN 128:293873
TI Human herpesvirus type 8 interleukin-6 homolog is functionally active on human myeloma cells
SO Blood (1998), 91(6), 1858-1863
CODEN: BLOOAW; ISSN: 0006-4971
AU Burger, Renate; Neipel, Frank; Fleckenstein, Bernhard; Savino, Rocco; Ciliberto, Gennaro; Kalden, Joachim R.; Gramatzki, Martin
AB Seroepidemiol. and polymerase chain reaction studies have strongly suggested that human herpesvirus type 8 (HHV-8) is associated with Kaposi's sarcoma, Castleman's disease, and body cavity-based lymphoma. The genome of HHV-8 harbors a viral analog of the interleukin-6 (IL-6) gene. The amino acid sequence of the viral IL-6 (vIL-6) protein is 24.7% identical to human IL-6 (hIL-6). IL-6 as a B-cell growth and differentiation factor is known to play an essential role in the pathophysiol. of B-cell tumors. Thus, it seems possible that virus-encoded IL-6 contributes to malignant growth of HHV-8-pos. B-cell lymphatic tumors. We have tested a preparation of HHV-8-derived IL-6 for the ability to promote the proliferation of the human myeloma cell line INA-6, which is strictly dependent on exogenous IL-6 for growth and survival. Viral IL-6 significantly induced DNA

synthesis of INA-6 cells, but required much more protein on a weight basis when compared with hIL-6 for maximal proliferation. The proliferative effect of vIL-6 was almost completely inhibited by a combination of anti-IL-6 receptor (IL-6R) and anti-gp130 antibodies or IL-6R superantagonist Sant7 and anti-gp130 antibodies. This report demonstrates that vIL-6 has proliferative activity on human cells and that the IL-6R and gp130 are involved in vIL-6 signaling in the myeloma cell line INA-6.

L11 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
 AN 1996:760040 CAPLUS
 DN 126:55664
 TI Human herpesvirus 8 encodes a homolog of interleukin-6
 SO Journal of Virology (1997), 71(1), 839-842
 CODEN: JOVIAM; ISSN: 0022-538X
 AU Neipel, Frank; Albrecht, Jens-Christian; Ensser, Armin; Huang, Yao-Qi; Li, Jian Jun; Friedman-Kien, Alvin E.; Fleckenstein, Bernhard
 AB Kaposi's sarcoma is a multifocal lesion that is reported to be greatly influenced by cytokines such as interleukin-6 (IL-6) and oncostatin M. DNA sequences of a novel human gammaherpesvirus, termed human herpesvirus 8 (HHV-8) or Kaposi sarcoma-associated herpesvirus, have been identified in all epidemiol. forms of Kaposi's sarcoma with high frequency. The presence of HHV-8 DNA is also clearly associated with certain B-cell lymphomas (body cavity-based lymphomas) and multicentric Castleman's disease. Sequence anal. of a 17-kb fragment revealed that adjacent to a block of conserved herpesvirus genes (major DNA-binding protein, glycoprotein B, and DNA polymerase), the genome of HHV-8 encodes structural homolog of IL-6. This cytokine is involved not only in the pathogenesis of Kaposi's sarcoma but also in certain B-cell lymphomas and multicentric Castleman's disease. The viral counterpart of IL-6 (vIL-6) has conserved important features such as cysteine residues involved in disulfide bridging or an amino-terminal signal peptide. Most notably, the region known to be involved in receptor binding is highly conserved in vIL-6. This conservation of essential features and the remarkable overlap between diseases associated with HIV-8 and diseases associated with IL-6 dysregulation clearly suggest that vIL-6 is involved in HHV-8 pathogenesis.

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L5 1 S L4 AND PY<=1996
L6 40 FOCUS L4 1-

=> d an ti so au ab pi l6 38 21 17 1

L6 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:89360 CAPLUS
DN 128:166368
TI The interleukin 6 of human herpesvirus 8 and its use in diagnostics and
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SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
IN Fleckenstein, Bernhard; Albrecht, Jens-Christian; Neipel, Frank;
Friedman-Kien, Alvin; Huang, Yao-Qi
AB Human herpesvirus 8 is found to carry a gene for an interleukin 6 that can
bind to the interleukin 6 receptor. The interleukin and the gene encoding
can be used in the diagnosis and treatment of a number of diseases including:
Kaposi sarcoma, Castleman's disease, multiple myeloma, kidney cell
carcinoma, mesangial proliferative glomerulonephritis or B cell lymphoma.
The protein may be manufactured by expression of the cloned gene.
PATENT NO. KIND DATE APPLICATION NO. DATE

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9803657	A1	19980129	WO 1996-EP3199	19960719
W: US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 912742	A1	19990506	EP 1996-927558	19960719
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE				
US 2004228838	A1	20041118	US 2004-828343	20040421

L6 ANSWER 21 OF 40 MEDLINE on STN
AN 97138401 MEDLINE
TI Human herpesvirus 8 encodes a homolog of interleukin-6.
SO Journal of virology, (1997 Jan) 71 (1) 839-42.
Journal code: 0113724. ISSN: 0022-538X.
AU Neipel F; Albrecht J C; Ensser A; Huang Y Q; Li J J; Friedman-Kien A E;
Fleckenstein B
AB Kaposi's sarcoma is a multifocal lesion that is reported to be greatly
influenced by cytokines such as interleukin-6 (IL-6) and oncostatin M. DNA sequences of a novel human
gammaherpesvirus, termed human herpesvirus 8 (HHV-8) or Kaposi
sarcoma-associated herpesvirus, have been identified in all
epidemiological forms of Kaposi's sarcoma with high frequency. The
presence of HHV-8 DNA is also clearly associated with certain B-cell
lymphomas (body cavity-based lymphomas) and multicentric Castleman's
disease. Sequence analysis of a 17-kb fragment revealed that adjacent to
a block of conserved herpesvirus genes (major DNA-binding protein,
glycoprotein B, and DNA polymerase), the genome of HHV-8 encodes
structural homolog of IL-6. This cytokine is involved
not only in the pathogenesis of Kaposi's sarcoma but also in certain
B-cell lymphomas and multicentric Castleman's disease. The viral
counterpart of IL-6 (vIL-6) has
conserved important features such as cysteine residues involved in
disulfide bridging or an amino-terminal signal peptide. Most notably, the
region known to be involved in receptor binding is highly
conserved in vIL-6. This conservation of essential
features and the remarkable overlap between diseases associated with HHV-8
and diseases associated with IL-6 dysregulation
clearly suggest that vIL-6 is involved in HHV-8
pathogenesis.

L6 ANSWER 17 OF 40 MEDLINE on STN
 AN 2003592109 MEDLINE
 TI Molecular mechanisms for viral mimicry of a human cytokine: activation of gp130 by HHV-8 interleukin-6.
 SO Journal of molecular biology, (2004 Jan 9) 335 (2) 641-54.
 Journal code: 2985088R. ISSN: 0022-2836.
 AU Boulanger Martin J; Chow Dar-chone; Brevnova Elena; Martick Monika; Sandford Gordon; Nicholas John; Garcia K Christopher
 AB Kaposi's sarcoma-associated herpesvirus (KSHV, or HHV-8) encodes a pathogenic viral homologue of human interleukin-6 (IL-6). In contrast to human IL-6 (hIL-6), viral IL-6 (vIL-6) binds directly to, and activates, the shared human cytokine signaling receptor gp130 without the requirement for pre-complexation to a specific alpha-receptor. Here, we dissect the biochemical and functional basis of vIL-6 mimicry of hIL-6. We find that, in addition to the "alpha-receptor-independent" tetrameric vIL-6/gp130 complex, the viral cytokine can engage the human alpha-receptor (IL-6Ralpha) to form a hexameric vIL-6/IL-6Ralpha/gp130 complex with enhanced signaling potency. In contrast to the assembly sequence of the hIL-6 hexamer, the preformed vIL-6/gp130 tetramer can be decorated with IL-6Ralpha, post facto, in a "vIL-6-dependent" fashion. A detailed comparison of the viral and human cytokine/gp130 interfaces indicates that vIL-6 has evolved a unique molecular strategy to interact with gp130, as revealed by an almost entirely divergent structural makeup of its receptor binding sites. Viral IL-6 appears to utilize an elegant combination of both convergent, and unexpectedly divergent, molecular strategies to oligomerize gp130 and activate similar downstream signaling cascades as its human counterpart.

L6 ANSWER 1 OF 40 MEDLINE on STN
 AN 2001198464 MEDLINE
 TI Detection of direct binding of human herpesvirus 8-encoded interleukin-6 (vIL-6) to both gp130 and IL-6 receptor (IL-6R) and identification of amino acid residues of vIL-6 important for IL-6R-dependent and -independent signaling.
 SO Journal of virology, (2001 Apr) 75 (7) 3325-34.
 Journal code: 0113724. ISSN: 0022-538X.
 AU Li H; Wang H; Nicholas J
 AB Human herpesvirus 8 (HHV-8) is associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castlemann's disease; in all of these diseases, interleukin-6 (IL-6) has been implicated as a likely mitogenic and/or angiogenic factor. HHV-8 encodes a homologue of IL-6 (viral IL-6 [vIL-6]) that has been shown to be biologically active in several assays and whose activities mirror those of its mammalian counterparts. Like these proteins, vIL-6 mediates its effects through the gp130 signal transducer, but signaling is not dependent on the structurally related IL-6 receptor (IL-6R; gp80) subunit of the receptor-signal transducer complex. However, as we have shown previously, IL-6R can enhance vIL-6 signal transduction and can enable signaling through a gp130 variant (gp130.PM5) that is itself unable to support vIL-6 activity, indicating that IL-6R can form part of the signaling complex. Also, our analysis of a panel of vIL-6 mutants in transfection experiments in Hep3B cells (that express IL-6R and gp130) showed that most were able to function normally in this system. Here, we have used in vitro vIL-6-receptor binding assays to demonstrate direct binding of vIL-6 to both gp130 and IL-6R and vIL-6-induced gp130-IL-6R complex formation, and we have extended our functional analyses of the vIL-6 variants to identify residues important for IL-6R-independent and IL-6R-dependent signaling through native gp130 and gp130.PM5, respectively.

These studies have identified residues in vIL-6 that are important for IL-6R-independent and IL-6R-mediated functional complex formation between vIL-6 and gp130 and that may be involved directly in binding to gp130 and IL-6R.